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For: PERFUSION MEASUREMENT USING CONTRAST AGENTS
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Perfusion measurement using contrast agents

Jeff Powers, Oct. 4, 1995

Background and prior art

The use of contrast agents to measure tissue perfusion has been widely discussed. Indicator dilution measurements are used in other imaging modalities to measure flow rates by injecting a bolus of a tracer and measuring the concentration downstream of the injection site. The integral under the curve gives a measure of the perfusion. This technique has been documented in many fields. A key element in this type of analysis is the transit time of the agent, or the time between injection and arrival of the agent at the measurement site.

Intravenously injectable contrast agents are being developed for ultrasound that reliably pass the pulmonary circulation and can be detected with ultrasound throughout the vascular system. These agents typically consist of a microbubble of gas (air, or a less soluble gas such as a fluorocarbon) stabilized or encapsulated to prevent rapid dissolution. Many researchers have attempted to quantify perfusion by transit time methods with ultrasound contrast agents. With an IV injection, however, the bolus get so spread out in passing through the lungs and heart that by the time it reaches the measurement site it is difficult to accurately measure the time of arrival. This is illustrated in Figs. 1 and 2. A more accurate method would use arterial injection close to the region of interest, but arterial injection is a much more invasive and dangerous procedure and is avoided unless absolutely necessary.

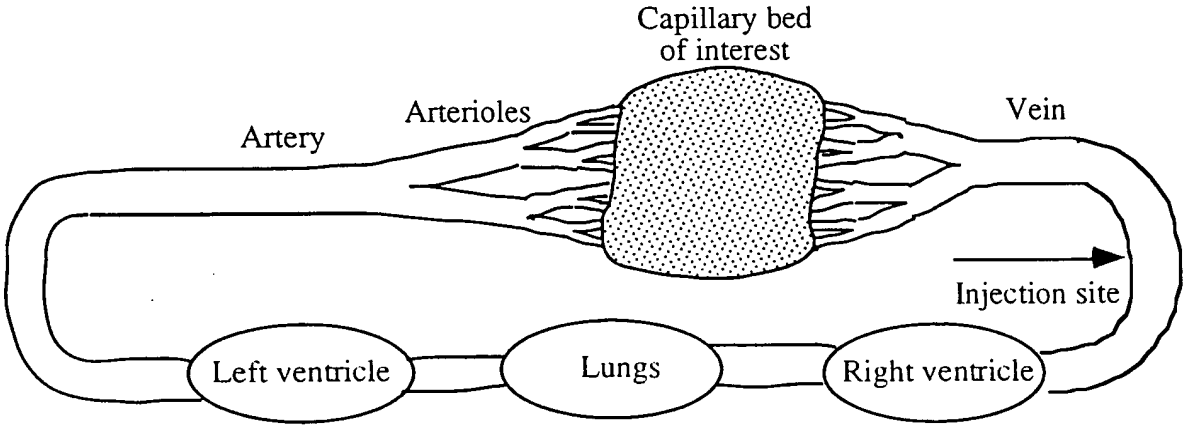


Fig. 1. Schematic diagram of circulatory system with tissue bed of interest.

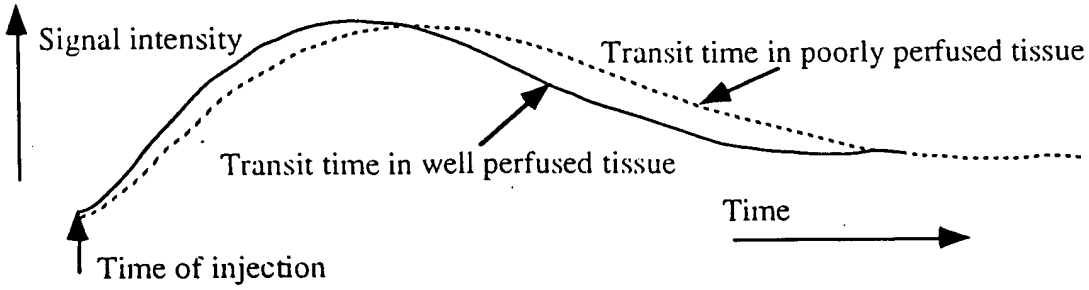


Fig. 2. Time / intensity curves for well and poorly perfused tissue.

It has been suggested that perfusion can be measured by estimating of the amount of blood in a region of interest by measuring the amount of contrast. This works for tissue that is totally infarcted, or the feeding artery is completely occluded and there is no perfusion to the tissue. However, for tissue that is marginally supplied, the blood volume is the same downstream of a stenosis, but the flow rate through the tissue is low. In some cases the blood volume is even higher than in normally perfused tissue due to autoregulation and hyperemia. While ultrasound Doppler can measure velocities, the velocity of blood at the arteriole and capillary level is very low and in random directions so that the Doppler angle cannot be reliably measured, making velocity measurement subject to large errors.

The invention

It has been demonstrated that some ultrasound contrast agents are destroyed by the incident ultrasound used to detect them using approved power levels. This has previously been considered a drawback, requiring lower power levels, lower frame rates, or cardiac gating (acquiring only one frame every heart cycle). The invention is to use the destruction of the bubbles to more accurately measure tissue perfusion using a technique similar to the above transit time analysis.

The general concept is that the microbubbles are destroyed within the region of interest, and the rate at which they reappear gives a measure of perfusion. This can lead to a number of different measurement techniques depending on the contrast agent and the characteristics of the tissue of interest. Two examples will be given here, but there are many other related techniques as well.

Example 1: This first example best illustrates the concept. The agent is infused slowly so that there is a constant supply of agent to the region of interest. It is assumed that the agent can be completely destroyed with one frame at high power, but concentration can be monitored at low power without destroying the agent.

In this case, the system acquires one frame of data using high power which completely destroys the microbubbles within the scanplane. Then, the time it takes for the agent to reappear to the level measured prior to the high power frame gives a measure of the time required to flush the region of interest and reperfuse it with fresh blood. Since the agent is only destroyed within the scanplane, the time required for reperfusion is much less than that required for an IV injected bolus to reach the region of interest, making the time measurement far more accurate. A diagram of the physiology is shown in Fig. 3, and a transit time diagram is shown in Fig. 4.

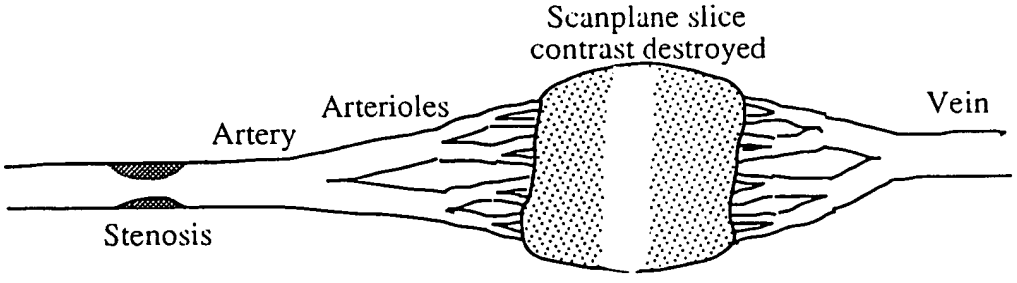


Fig. 3. Region of interest following high power frame. Contrast destroyed in scanplane.

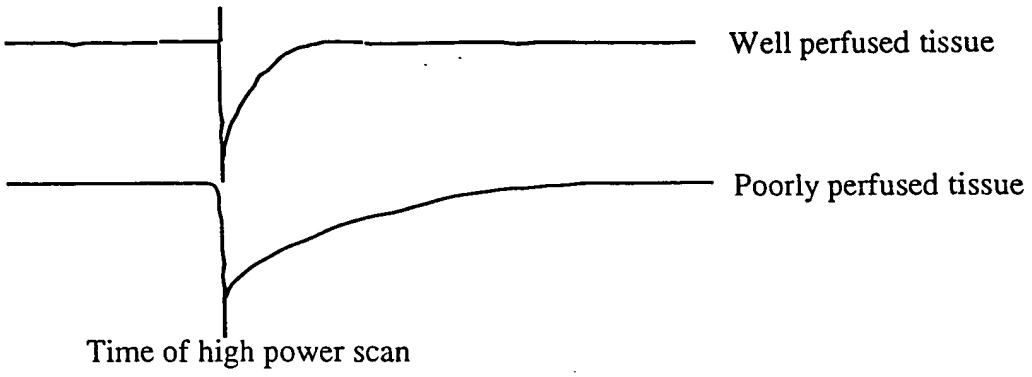


Fig. 4. Time / intensity curves for tissue in scanplane following high power scan.

Example 2: The agent is again infused, but it cannot be monitored at low power without microbubble destruction.

In this case, imaging is stopped for a period of time to allow the contrast to completely perfuse the tissue of interest. Then a single image is acquired for reference to show the organ fully perfused with contrast. A frame rate is selected which allows the signal from well perfused tissue to return close to baseline. Then, when the organ is imaged, normally perfused tissue will appear nearly as bright as the stored single image, but poorly perfused tissue will appear dim due to the slow reperfusion.

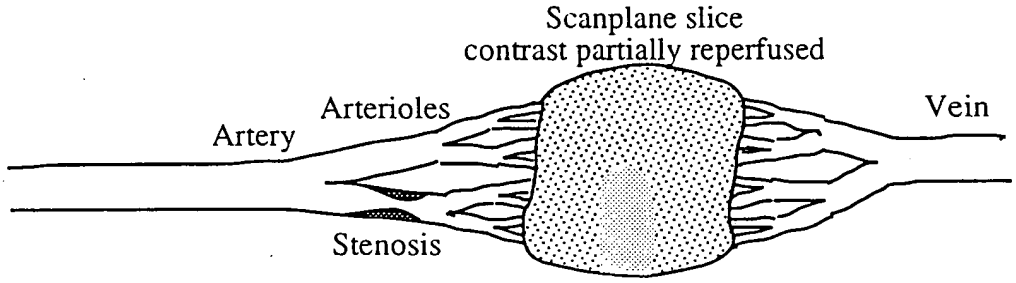


Fig. 5. Tissue imaged to accentuate slowly reperfusing tissue.

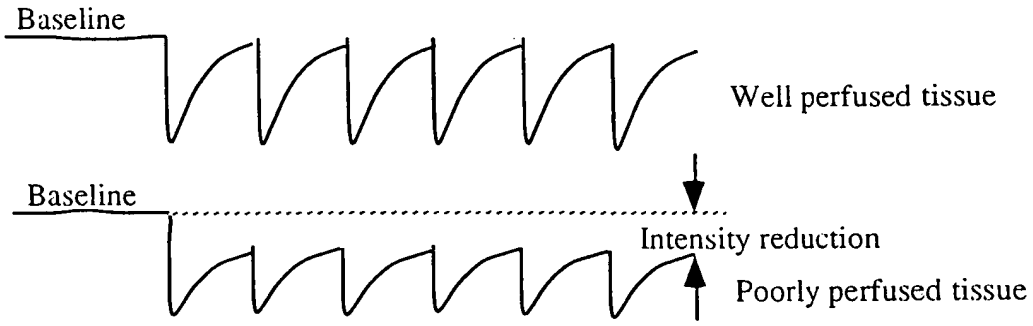


Fig. 6. Time intensity curves for periodic scanning sequence.

Signal Processing for Microbubble Detection and Clutter Suppression

JJ Hwang, 10/3/95

To detect the harmonic response of microbubbles, the harmonic component in the incident pressure wave must be suppressed. A novel signal processing technique is proposed that echoes from a sequence of pulses with alternate polarity are processed to detect microbubbles and suppress clutter.

Microbubbles Detection

Narrowband Excitation

Based on the analytical solution of the dynamic motion of microbubbles(1, 2), the primary component of the backscattering pressure magnitude is linearly proportional to the incident pressure and the harmonic component is quadratically proportional to the incident pressure p_i.

Or $p_s(\omega) \propto p_i$ and $p_s(2\omega) \propto p_i^2$.

Thus, neglecting the higher order terms, one may write the backscattering pressure magnitude $p_B(\omega)$ from microbubble in a generic form

$$p_B(\omega) = k_1(\omega)p + k_2(\omega)p^2; \quad \text{.....(1)}$$

where k_1 and k_2 are parametrically related to the acoustic properties of the microbubble such as size, viscosity, surface tension, ambient pressure, etc.

Let us now assume the microbubble are excited by two narrow band signals at different time with same magnitude p at same frequency ω, however, are opposite in polarity: $p_{i1} = p\cos\omega t$ and $p_{i2} = -p\cos\omega t$.

Then the backscattered pressure excited from $p_{i1} = p\cos\omega t$ is

$$p_{B1}(\omega,t) = k_1(\omega,t)p + k_2(\omega,t)p^2; \quad \text{.....(2)}$$

from $p_{i2} = -p\cos\omega t$ is

$$p_{B2}(\omega,t+\delta t) = k_1(\omega,t+\delta t)p + k_2(\omega,t+\delta t)p^2 \quad \text{..... (3)}$$

Then the total backscattered pressure magnitude may be obtained by summing Equations (2) and (3),

$$S = p_{B1} + p_{B2} = \left(k_1(\omega,t) - k_1(\omega,t+\delta t)\right)p + \left(k_2(\omega,t) + k_2(\omega,t+\delta t)\right)p^2 \quad \text{.....(4)}$$
$$\approx 2k_2(\omega)p^2$$

Equation (4) shows the primary component is eliminated if $k_1(\omega)$ and $k_2(\omega)$ do not change in time duration of δt, when δt is small.

Quasi-Stationarity Assumption

Assume the backscattering from microbubbles is quasi-stationary over T, where T in the pulse repetition interval. In other words, the average nonlinear acoustic properties are not changed over time T. Or

$$E\{k_1(\omega,t)\} \equiv E\{k_1(\omega,t+T)\}$$

and

$$E\{k_2(\omega,t)\} \equiv E\{k_2(\omega,t+T)\}.$$

Then the relationship of Equation (4) will hold by summing the pulse echoes from two pulses which are time-diverse in T.

Quasi-stationarity is valid assumption for slow perfused flow.

Wideband Excitation

When the bandwidth of the incident pressure wave is wide, the wideband excitation wave $P(t)$ may be represented by a Fourier series

$$P(t) = \sum_i A(\omega_i)\cos\omega_i t$$

Thus the backscattered pressure magnitude of the microbubbles from $P(t)$ may be written as

$$P_{B1} = \sum_i k_1(\omega_i)A(\omega_i) + \sum_i k_2(\omega_i)A^2(\omega_i) \quad \text{.....(5)}$$

and the backscattered pressure magnitude of the microbubbles from $-P(t)$ may be written as

$$P_{B2} = -\sum_i k_1(\omega_i)A(\omega_i) + \sum_i k_2(\omega_i)A^2(\omega_i); \quad \text{.....(6)}$$

Summing Equations (5) and (6), one may obtain

$$S = p_{B1} + p_{B2} = 2\sum_i k_2(\omega_i)A^2(\omega_i);\quad\quad(7)$$

Again, the harmonic component is extracted and the primary component is eliminated.

Clutter Suppression

Let us assume the nonlinearity in tissues is negligible. Since the backscattered pressure in a linear medium is linearly proportional to the incident pressure wave, the polarity of the backscattered wave will be changed as the polarity of the incident pressure wave is changed. Assuming the tissue is relatively stationary during the period of two consecutive pulsing, clearly, summing the pulse echoes from consecutive pulses with opposite polarity will be canceled. Thus clutter will be suppressed.

Multiple Pulse Processing

The concept of summing the pulse echoes from two pulses of opposite polarity may be generalized into processing echoes from multiple pulses with alternate polarity to maximize the sensitivity and minimize the variance. Assuming the tissue is stationary during a period of n PRI.

Let the pulse sequence be

$$P = \{p \quad -p \quad p \quad -p \quad p \quad -p \quad \bullet \quad \bullet \quad -p \quad p\}$$

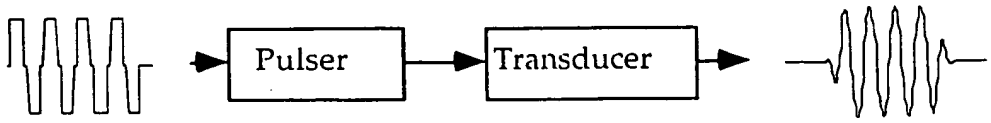
and the pulse echoes be

$$E = \{E_1 \quad E_2 \quad E_3 \quad E_4 \quad E_5 \quad E_6 \quad \bullet \quad \bullet \quad \bullet \quad E_n\}$$

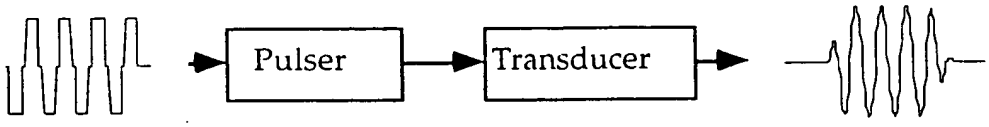
Accumulating the partial sum of the consecutive pair of echoes result in

$$S = \sum_{j=1}^{n-1} E_j + E_{j+1} = 2(n-1)\sum_i k_2(\omega_i)A^2(\omega_i)$$

Excitation n



Excitation n+1



Implementation

In the HDI, both the duty cycle and the polarity of the bipolar square excitation signal are programmable(3). One may toggle the polarity of the transmit signal in the ASIC for alternate polarity pulsing. The receive echoes from consecutive pulses may then be integrated in the synthetic aperture buffer before harmonics filtering for microbubble detection.

References;

1. Charles C. Church, "The effect of an elastic solid surface layer on the radial pulsation of gas bubbles," JASA, Vol 97, No. 3, March 1995. pp. 1510-1521.

2. D. L. Miller, "Ultrasonic detection of resonant cavitation bubbles in a flow tube by their second-harmonic emissions," Ultrasonics, Sept., 1981, pp. 217-224.

3. HDI Document, No. 2070-0326-01